Multi-genetic events collaboratively contribute to Pten-null leukaemia stem-cell formation.

Journal: Nature

Publication Year: 2008

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PubMed link: 18463637

Funding Grants: CIRM Type I Comprehensive Training Program

Public Summary:

Scientific Abstract:
Cancer stem cells, which share many common properties and regulatory machineries with normal stem cells, have recently been proposed to be responsible for tumorigenesis and to contribute to cancer resistance. The main challenges in cancer biology are to identify cancer stem cells and to define the molecular events required for transforming normal cells to cancer stem cells. Here we show that Pten deletion in mouse haematopoietic stem cells leads to a myeloproliferative disorder, followed by acute T-lymphoblastic leukaemia (T-ALL). Self-renewable leukaemia stem cells (LSCs) are enriched in the c-Kit(mid)CD3(+)Lin(-) compartment, where unphosphorylated beta-catenin is significantly increased. Conditional ablation of one allele of the beta-catenin gene substantially decreases the incidence and delays the occurrence of T-ALL caused by Pten loss, indicating that activation of the beta-catenin pathway may contribute to the formation or expansion of the LSC population. Moreover, a recurring chromosomal translocation, T(14;15), results in aberrant overexpression of the c-myc oncogene in c-Kit(mid)CD3(+)Lin(-) LSCs and CD3(+) leukaemic blasts, recapitulating a subset of human T-ALL. No alterations in Notch1 signalling are detected in this model, suggesting that Pten inactivation and c-myc overexpression may substitute functionally for Notch1 abnormalities, leading to T-ALL development. Our study indicates that multiple genetic or molecular alterations contribute cooperatively to LSC transformation.